

Study in Finland Suggests Vitamin E Prevents Prostate Cancer

The latest analysis from a large prevention trial conducted by the National Cancer Institute (NCI) and the National Public Health Institute of Finland shows that long-term use of a moderate-dose vitamin E supplement substantially reduced prostate cancer incidence and deaths in male smokers. The report was published in the March 18, 1998, issue of the *Journal of the National Cancer Institute*, and the lead author is Olli P. Heinonen, M.D., D.Sc., of the Department of Public Health, University of Helsinki, Finland.

This report from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study) showed that 50- to 69-year-old men who took 50 mg of alpha-tocopherol (a form of the antioxidant vitamin E) daily for 5 to 8 years had 32 percent fewer diagnoses of prostate cancer and 41 percent fewer prostate cancer deaths compared with men who did not receive vitamin E. This dose of vitamin E is equal to about 50 international units (the measure more commonly used with supplements) and is about three times the Recommended Dietary Allowance. The 29,133 male smokers from Finland were randomly assigned to receive alpha-tocopherol, beta-carotene (20 mg), or a placebo (an inactive pill that looked like the vitamin) daily.

“These results give hope that a simple intervention may one day help reduce a man’s chances of developing and dying from prostate cancer,” said Demetrius Albanes, M.D., one of NCI’s lead investigators on the study. “But it is important that other studies be done to confirm the beneficial effects of vitamin E. The ATBC Study and similar trials have shown us that

supplements are not necessarily magic bullets and, more importantly, that what may be a beneficial supplement for some people may be harmful to others,” said Albanes, who is in the Cancer Prevention Studies Branch of NCI’s Division of Clinical Sciences.

As an example, he noted that earlier results from the ATBC Study showed that men who took the beta-carotene supplement had 16 percent more cases of lung cancer and 14 percent more lung cancer deaths than those who did not take beta-carotene. Men who drank large amounts of alcohol, and who took the beta-carotene, had higher rates of lung cancer than men who drank less alcohol.

In the current analysis, men taking beta-carotene supplements had more prostate cancer as well, but this increase was not statistically significant and was limited to men who drank alcohol. Men taking both nutrients (beta-carotene and vitamin E) had fewer cases of prostate cancer compared with men on placebo.

In men taking the vitamin E, there was a reduction in clinically detectable prostate cancers beginning within 2 years of starting the supplement—a result which suggests to Philip R. Taylor, M.D., Sc.D., chief of NCI’s Cancer Prevention Studies Branch, that vitamin E may be blocking a prostate tumor’s progression to a more aggressive state. Most older men have microscopic areas of cancer in their prostate, few of which will progress to life-threatening disease.

“We know that prostate cancer develops first as latent cancer that can’t be detected clinically,” said Taylor. “For some men, these tumors are transformed from subclinical cancer—which may never affect a man’s health—into aggressive disease. We think vitamin E is working by blocking the changeover from these more benign tumors to potentially life-threatening disease.”

The investigators do not think that vitamin E affected symptoms that would cause a man to have medical attention, which would lead to a diagnosis of cancer. Overall, men taking vitamin E had fewer diagnoses of later stage cancers than men not taking the supplement. The number of cancers diagnosed at earlier stages, when symptoms are few, was equivalent between supplement and placebo groups.

Prostate-specific antigen (PSA) testing was not common in Finland at the time of the study, and no other screening tests for prostate cancer were done as part of the ATBC Study. Most men diagnosed with prostate cancer had visited their physician with a complaint of urinary difficulties, while others sought medical care for other reasons but mentioned urinary problems, which then were evaluated. Blood samples were taken from the ATBC participants during the study, and using these, an analysis of the value of blood PSA levels in predicting prostate cancer is under way.

In the United States, prostate cancer is the most frequently diagnosed cancer in males, with 184,500 cases expected in 1998 along with 39,200 deaths. African American men have the highest rates of prostate cancer in the United States.

References

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Questions and Answers About Prostate Cancer Incidence and Mortality in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study

1. What is the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study?

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, or ATBC Study, was a chemoprevention trial conducted by the National Cancer Institute (NCI) and the National Public Health Institute of Finland. The purpose of the study was to see if certain vitamin supplements would prevent lung cancer and other cancers in a group of 29,133 male smokers in Finland. The 50- to 69-year-old participants took a pill containing 50 milligrams (mg) alpha-tocopherol (a form of vitamin E), 20 mg beta-carotene (a precursor of vitamin A), both, or a placebo (an inactive pill that looked like the vitamin) daily for 5 to 8 years.

2. What is a chemoprevention trial?

A chemoprevention trial is a type of clinical trial, which is a research study conducted with people. In a cancer chemoprevention trial, natural or man-made substances are tested to see if they prevent cancer. The people who participate in such a study are healthy or are at risk of developing cancer, or in some studies, people who have been treated for cancer and are at a risk of developing a second cancer.

3. What were the results of the ATBC Study?

In 1994 and 1996, the ATBC researchers reported that 16 percent more lung cancers were diagnosed and 14 percent more lung cancer deaths occurred in study participants taking beta-carotene. Vitamin E had no effect on lung cancer.

In the new report, ATBC researchers have shown that the participants taking vitamin E had 32 percent fewer cases of prostate cancer and 41 percent fewer deaths from prostate cancer.

4. Why was the ATBC Study conducted in Finland?

The study was conducted in Finland because of the high lung cancer rates in men in that country, which are due primarily to cigarette smoking. Furthermore, Finland has a clinic system for the screening and treatment of lung diseases (mainly tuberculosis) through which the recruited population of smokers could participate in the study. Finland also has a national cancer registry, which keeps track of all the cancer cases identified in that country, a vital measurement for the large trial.

5. Why was the trial conducted only in men?

Finnish women were not included in the study because their rate of lung cancer was substantially lower than the rate for Finnish men. In 1985, the annual age-adjusted lung

cancer rate for Finnish men was 67 cases per 100,000 men and for women the rate was 8 cases per 100,000 women.

6. Are the ATBC Study results applicable to Americans?

As a whole, the white men of Finland are similar to white men in the United States, and live similar Western lifestyles. However, in Finland the population is very uniform, with few ethnic and racial differences, so the relationship of these study results to specific minorities is less clear.

7. How do prostate cancer rates compare in U.S. men and Finnish men?

Using world standardized rates, the incidence rate of prostate cancer in the United States was 118.6 per 100,000 in 1994, including all races. The U.S. mortality rate was 17.3 per 100,000. In Finland, the 1995 incidence rate was 61.4 per 100,000 and the death rate was 17.9 per 100,000.

8. Why are prostate cancer incidence rates higher in the United States?

Although there are no clear answers, prostate cancer incidence rates in the United States may be higher in part because of the popularity of prostate-specific antigen (PSA) testing, which identifies cancers that cannot be found by clinical exam. PSA testing for early detection of prostate cancer is generally not done in Finland. Prostate cancer is also a disease of aging and affluence, and historically Finns had a lower life expectancy and standard of living than Americans. Currently, Finns and Americans share very similar lifestyles.

9. What causes prostate cancer?

The causes of prostate cancer are not yet understood. Age is a factor: most cases are diagnosed in men over age 55 years. Some families have higher incidence of prostate cancer, suggesting inherited susceptibility may influence the development of the disease. Hormones, including testosterone, may play a role. Many other possible factors may be involved, but are not proven or not well understood—men who have had vasectomies, farmers, workers exposed to the metal cadmium, workers in the rubber industry, and smokers may have a greater chance of developing prostate cancer.

Diets high in fat have been suggested to increase risk, while diets high in fruits and vegetables seem to decrease risk. A recent study suggested that supplements of selenium may reduce the risk of prostate cancer.

10. How does the normal Finnish diet compare with the U.S. diet?

The average Finnish diet used to be very high in saturated fat and low in fruits and vegetables. At the time the ATBC Study began, the fat content of the Finnish diet was about 38 percent of total calories. However, the national average fat intake has decreased

to about 34 percent of calories from fat, equal to the current U.S. average. The Finns also eat a lot of whole-grain products, like dark rye breads, which gives them a higher fiber intake, and they eat more dairy products. Dietary vitamin E intake is somewhat lower in Finland than in the United States (10 mg versus 17 mg per day).

11. Why were vitamin E and beta-carotene chosen for this trial?

Vitamin E and beta-carotene were chosen because epidemiologic studies have linked high dietary intake and high serum levels of these micronutrients to a reduced risk of cancer, particularly lung cancer. Both are antioxidants, compounds that may prevent carcinogens from damaging DNA.

12. How might vitamin E protect against prostate cancer?

The mechanisms by which vitamin E may reduce prostate cancer risk are not clear. Vitamin E is an antioxidant. Antioxidants are compounds that may prevent carcinogens from damaging DNA. In addition to its antioxidant activity, there are a number of possible mechanisms by which vitamin E may be working: vitamin E affects cell membranes, may inhibit the proliferation of cells, may stimulate the immune system or alter sex hormones, and could play a role in inhibiting or increasing apoptosis (programmed cell death). It also plays a role in inducing differentiation (the maturing of cells) and protecting the metabolic pathways that rid the body of toxins.

13. What doses of these supplements were given in the ATBC Study?

The dose of vitamin E was 50 mg per day of synthetic dl-alpha-tocopheryl acetate, which is equal to 50 international units (IU) of vitamin E. Most multivitamins have about 30 IU of vitamin E, and singular supplements most often have a minimum of 100 IU of vitamin E.

The dose of beta-carotene was 20 mg per day of synthetic beta-carotene. The men in the study took one pill each day, which contained vitamin E, beta-carotene, both, or neither.

14. Did vitamin E have any effect on other causes of death?

Overall, the number of deaths in men taking vitamin E was similar to men not taking vitamin E.

The men taking vitamin E were found to have fewer deaths from ischemic heart disease and ischemic stroke (a deficit of blood to the brain due to a constriction of a blood vessel), but more deaths due to all cancers and hemorrhagic stroke (a deficit of blood to the brain due to the rupture of a blood vessel).

15. What foods are major sources of alpha-tocopherol (vitamin E)?

Vitamin E is found mainly in oils, such as vegetable oils, and in nuts and grains. The amount in the U.S. diet varies, but is estimated to be about 17 mg per day. The top sources of vitamin E in the U.S. diet are salad dressings and mayonnaise; margarine; ready-to-eat cereals; cakes, cookies, and donuts; tomatoes; and eggs.

16. Should Americans take vitamin E supplements?

NCI has never recommended that Americans take supplements. The results of the ATBC Study, while promising, do not answer whether vitamin E supplements would be able to reduce the risk of prostate cancer in men of varying race and ethnicity and in nonsmokers. There is also concern that men taking vitamin E in this study had more of one type of stroke than men who did not take vitamin E. While the number of men in the ATBC Study who had this type of stroke (hemorrhagic stroke) was small, this possible side effect of vitamin E supplementation needs careful study.

17. Should Americans avoid taking beta-carotene supplements?

The results from the ATBC Study and the Beta-Carotene and Retinol Efficacy Trial (CARET) suggest that smokers should avoid taking beta-carotene supplements. The best advice for smokers who want to reduce their risk of lung cancer and many other cancers is still the most direct: Stop smoking.

The results of the only large-scale study of beta-carotene in primarily nonsmoking men, the Physicians' Health Study, showed no benefit or harm from taking beta-carotene supplements every other day for 12 years. For all Americans who wish to reduce their risk of cancer, a low-fat diet with plenty of fruits, vegetables, and whole grains remains the choice to make.

18. How much did the study cost?

NCI allocated about \$20 million over 10 years for the trial, with a similar sum contributed by the government and research institutions in Finland. In addition, F. Hoffmann-LaRoche, Ltd., a pharmaceutical company based in Basel, Switzerland, supplied the 60 million pills the men took during the trial, without charge, at a cost to the company of about \$3 million.

19. What other large-scale chemoprevention studies are under way?

NCI has a number of different agents under study, including calcium, fiber, tamoxifen, finasteride, and others. The only ongoing large-scale study of vitamin E is the Women's Health Study, headed by researchers at Boston's Brigham and Women's Hospital.

In the Women's Health Study, which began in 1992, 40,000 healthy women age 50 and older were recruited to take combinations of 50 mg beta-carotene, 600 mg vitamin E,

100 mg aspirin, or placebos every other day. After disappointing results from other beta-carotene trials were announced in January 1996, the beta-carotene portion of the study was dropped. The women are being monitored for cancer and heart disease benefits.

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Sources of National Cancer Institute Information

Cancer Information Service

Toll-free: 1-800-4-CANCER (1-800-422-6237)

TTY (for deaf and hard of hearing callers): 1-800-332-8615

NCI Online

Internet

Use <http://www.cancer.gov> to reach NCI's Web site.

CancerMail Service

To obtain a contents list, send e-mail to cancermail@icicc.nci.nih.gov with the word "help" in the body of the message.

CancerFax® fax on demand service

Dial 301-402-5874 and listen to recorded instructions.

This fact sheet was reviewed on 3/18/98